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Review

# Inflammatory breast cancer: The pathologists' perspective

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ABSTRACT

Inflammatory breast cancer (IBC) is a clinico-pathological entity, which has specific features of inflammation and pathological evidence of cancer, most often involving dermal lymphatics. This review looks at IBC from the pathologists point of view. The diagnostic criteria and differential diagnosis are summarized first. The staging implications are described next. Despite the overall poor prognosis of IBC, it is heterogeneous in terms of most prognostic and predictive factors (such as histological type, grade, receptor status, intrinsic subtype, inflammatory infiltrate). It seems that some molecular features (genes expressed) are unique to IBC, and this may help to identify them as IBC at the molecular level. The key carcinogenetic pathways activated in IBC, the inflammatory pathways present in the disease as well as the relation of IBC to cancer stem cells are also briefly covered. Due to the relative rarity of IBC, preclinical trials are very important in the study of this entity, and models with stromal and microenvironmental elements are expected to outperform the traditional models without these features, as the microenvironment seems to be a key component of IBC.



Inflammatory breast cancer (IBC) is a special manifestation of breast cancer that is associated with extremely bad prognosis. After dealing with diagnostic criteria and recognition of the disease and its staging implications, the molecular background of this special presentation will be explored in this review.

## Diagnostic considerations

As the name implies, IBC combines the clinical presentation of breast carcinoma with signs of locoregional inflammation, and should therefore be differentiated from several forms of non-cancerous mastitis.

Mastitis in its acute (sudden onset and/or short duration) form is characterized by the symptoms described by Celsus and taught to generations of physicians over the centuries: rubor (redness due to active hyperaemia), calor (raised local temperature over the inflamed area), tumor (swelling and/or mass formation due to oedema) and dolor (pain). All these cardinal signs are assessed and best appreciated clinically, while only two of them may have histologic correlates: dilated capillaries can reflect the redness, but are not always seen, as active hyperaemia is a functional change which may disappear *ex vivo*. Dilated capillaries seen in biopsies from IBC are generally of the lymphatic type, and can be highlighted with lymphatic endothelium specific markers, such as D2-40, podoplanin and LYVE-1, and may contain tumour emboli. Substantial oedema leading to the peau d'orange appearance can be appreciated in tissue biopsies, but is not easy to discriminate from tissue processing artefacts, myxoid degenerative changes or simply loose connective tissue. It must also be noted that redness cannot be evaluated in people with pigmented skin, as the high melanin content of the skin may suppress the colour of capillary dilatation [1], although some changes in tint/tone can often be appreciated [2]. In contrast, neutrophils, the classic histologic feature of acute inflammations, are lacking in IBC.

Acute mastitis is generally caused by infectious agents, most often pyogenic bacteria, especially *Staphylococcus aureus*, entering the breast parenchyma through small skin disruptions, cracks caused by breastfeeding, eczema or mechanical irritation.

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Staphylococcal infections are prone to abscess formation, although other forms may lead to a more diffuse cellulitis as seen with *Streptococcal* infections. Timely systemic administration of antibiotics may alter the clinical course of acute mastitis and often prevent abscess formation [3]. Chronic forms of mastitis (with longer duration and less abrupt start) also exist and have symptoms overlapping with acute mastitis; their aetiology includes infectious (e.g. tuberculous mastitis, cystic neutrophilic granulomatous mastitis) and non-infectious causes (e.g. periductal/plasma cell mastitis, idiopathic granulomatous mastitis, autoimmune mastitis (e.g diabetic mastopathy)).

IBC by definition presents in the form of acute mastitis; the onset is abrupt. Experts have agreed that symptoms of inflammation should be present for no more than 6 months to allow for the diagnosis of IBC [4], but often the history is much shorter, and dates back to only a few weeks [5]. By definition, the erythema must involve at least one third of the breast [1]. On the basis of the previous considerations, it is not surprising that the inflammatory nature is diagnosed clinically (swelling, peau d'orange, enlargement, erythema, pain, which sometimes involves the axilla too), whereas the neoplastic nature is diagnosed by microscopy and often preceded by imaging. Most forms of mastitis (the common ones) respond to antibiotics, but those not responding to an adequate course of such treatment should undergo further investigations as to alternative causes of the inflammation: pathogens (including parasites) unresponsive to the given antibiotics [6–9], non-infectious causes mimicking cancer [10,11], or cancer itself. To render the diagnosis of IBC, microscopic verification of tumour emboli in the lymphatics of the skin and preferably the underlying invasive carcinoma itself is mandatory.

Many IBC cases lack a palpable lump on physical examination; in fact, this is the typical presentation. As concerns imaging, ultrasound (US) often outperforms mammography, and often highlights axillary lymph node involvement. Magnetic resonance imaging (MRI) is somewhat more sensitive than US. The most common findings on MRI are multiple, small, heterogeneously enhancing nodules along with diffuse skin thickening [12,13]. Whenever a mass lesion is visualized, a core needle biopsy should establish the diagnosis of an underlying cancer. Fine-needle aspiration may also have a role in establishing the diagnosis of IBC [2]. In a small series of 5 patients, the authors used a “tangential” technique to aspirate the superficial oedematous dermis, and have seen malignant cells in 4/5 cases of suspected IBC after aspirating all four quadrants; this diagnostic yield was greater than that of core needle biopsies of the skin [2]. If no lump can be visualized by US, or if core needle biopsy fails, it is common practice in our department to introduce a free needle into the dermis of patients with suspected IBC and let the pressure of the oedema bring out some fluid and accompanying cells which can be smeared for staining and microscopy; this approach has also led to the identification of IBC. Proving malignancy from regional axillary lymph nodes may also be sufficient in the context of IBC. Core needle biopsy may be preferred to fine needle aspirates in these cases, because it renders tissue samples better suited for histologic, immunohistochemical and molecular characterization of the tumour. It is advised to take several cores and embed them separately to allow prognostic and predictive marker (oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER2)) studies before primary systemic treatment and even further studies after surgery, if complete response occurs. If possible, tumour tissue should also be taken for biobanking.

Whenever the diagnosis of cancer is made in the setting of a sufficiently large (at least one third of the breast) inflammatory presentation, the diagnosis of IBC can be made with confidence, although secondary cancers which are rare in the breast have also been reported to imitate IBC [14–17].

It has long been debated whether or not dermal lymphatic invasion is a sine qua non for the diagnosis of IBC. Swelling is mainly due to lymphedema, i.e. to the obstruction of the lymph flow either due to lymphatic emboli and/or massive nodal obliteration. Although the finding of dermal lymphatic tumour emboli is common in IBC (up to 75% have proven lymphatic invasion in the dermis) and this finding strengthens the diagnosis, there is agreement that this is not required to establish the diagnosis of IBC [1] for which the clinical presentation is overriding. Punch biopsies are suitable to sample the dermis and discover lymphatic tumour emboli in many patients [18]. A minimum of two punch biopsies (2–8 mm in diameter) has been advised from the area demonstrating the most prominent discoloration [4] or peau d'orange sign [19]. Alternately, small incisional biopsies may lead to the same result. These samples also demonstrate skin thickening [18].

In summary, neither a breast cancer without the characteristic signs of IBC (rapid onset of erythema, enlargement, oedema with or without the peau d'orange sign, and/or warmth, with or without a palpable tumour, and involvement of at least a third of the breast) nor the listed symptoms of inflammation without a proven breast cancer qualify for IBC, the two ought to be together. Therefore, IBC is a clinico-pathological diagnosis [5,20–24] which requires a multidisciplinary approach for diagnosis [25].

## Staging implications, prognostic and predictive factors

IBC is considered to represent an advanced stage. It is coded as T4d (a category reserved for IBC) according to the TNM classification, which, however, does not make any distinction between other T4 categories and the T4d as determinant of stage. As a potential source of confusion, the T4b category, i.e. a cancer with extension to the skin defined as ulceration and/or satellite dermal nodules and/or oedema, includes the peau d'orange sign if it does not meet the criteria for IBC. All T4 cancers belong to (anatomic) stage IIIB, unless nodal involvement reaches N3 (stage IIIC) or distant metastasis is present (stage IV) [23,26]. The American Joint Committee on Cancer (AJCC) has also introduced prognostic stages into the last edition of the staging manual [23]. According to this, a T4N0-3M0, grade 1 tumour with a HER2 negative, but ER and PR positive status would be of stage IIIA, i.e. would be downstaged compared to its anatomic stage defined by the T, N and M categories alone. Nodal metastases are very common in IBC. An analysis of more than 750 cases from the Survival Epidemiology and End-Results database suggested that only 20% of the cases were node negative, and that nodal status was of prognostic impact even in IBC [27]. More than one third of the cases have 10 or more nodes involved, and are therefore in category pN3 [28].

Most locally advanced breast cancer (LABC) cases have skin involvement (pT4b or pT4c), which include ulceration, satellite cutaneous nodules or the peau d'orange sign, and/or histologic infiltration of the dermal lymphatics by tumour emboli. Localised inflammatory signs may also develop either as a result of ulceration and infection or as a result of tumour necrosis and/or stasis. Although peritumoural lymphatic invasion is commonly present, diffuse skin thickening and dermal lymphatic involvement is not a feature of LABC, which is clinically distinguished from IBC on the basis of the absent or limited inflammatory signs [18]. In parallel, ulceration and cutaneous nodules are not features of IBC [1]. In the rare case, when all the clinical features of IBC are present, and carcinoma is diagnosed as the disease behind the inflammatory signs, but the skin area involved is smaller than one third of the breast, it was suggested to classify the disease as T4b or T4c in the 7th edition of the AJCC Cancer staging manual [22], a suggestion that is missing from the 8th edition in use from January 2018 for unknown reasons [24]. However, as involvement of at least one

third of the breast is part of the definition of IBC, such cases should not be labelled as IBC for staging, even if one is tempted to treat them according to this diagnosis.

Although stage is not influenced by the presence of inflammatory signs, IBC is generally defined separately in the staging books. Clinical symptoms defining the entity have been differently worded in different editions. There are consistent parts of the definition, but the wording has also slightly changed over the years, at least as concerns the AJCC staging books (Table 1) [20–23,26,29,30]. The UICC TNM books have also a note saying that whenever the skin biopsy is negative for cancer, and there is no "localized measurable primary" carcinoma detected, the pathological staging category should be pTx for a cT4d tumour [29,30]. This is difficult to interpret, in the light of the pathological pT categories and clinical cT/T categories being identically defined, a measurable tumour size not being part of the definition of the T4d category, but the proof of carcinoma being essential for the diagnosis of IBC, i.e. T4d.

These staging rules suggest that IBC is perceived as an advanced stage disease which, on the base of its clinical presentation, should however be distinguished from LABCs having a long history and a slower development. There are data to suggest that IBC differs from other advanced stage breast cancers in several aspects.

According to a recent analysis of nearly 600 IBC cases from the National Cancer Database, IBC can represent either ER and/or PR positive tumours with a HER2 negative (39%) or positive (16.5%) status, or HER2 positive, ER and PR negative tumours (18.9%) or triple negative carcinomas (25.6%) [31]. Compared to non-IBC, the more aggressive, ER negative phenotypes thereby not surprisingly dominate [32]. HER2 positive cases had the best survival, probably due to effective anti-HER2 targeted treatments [31,33,34], whereas hormone receptor positive tumours had worse outcome [31,35], probably due to their moderate response to chemotherapy. Even with aggressive treatments, patients with triple negative IBC have the worst survival of all [34]. Patients with triple negative cancers presenting as IBC have worse survival than those with non-inflammatory presentation [36], indicating that they respond less well to chemotherapy than their non-IBC counterparts. Some authors have not found survival differences between IBCs of different phenotypes classified on the basis of ER, PR and HER2 status [37].

As patients with IBC are often relatively young and the diagnosis of breast cancer in the young is part of the indication for susceptibility gene testing, the mutational status of the BRCA1 and BRCA2 genes, the most common susceptibility genes for breast cancer, may be of special interest. A large series from the MD Anderson Cancer Center including 105 IBC and 1684 non-IBC with BRCA genetic testing results suggests that there are no differences between the two presentations, i.e. IBC is not associated with BRCA1 or BRCA2 pathogenic variants [38].

As implied by the extreme aggressiveness of IBC, it is not surprising that the majority of patients have histological grade 3 tumours; although a small minority do have grade 1 carcinomas [28,39]. Most IBC are carcinomas of no special type, but lobular carcinomas and other special type carcinomas have also been reported as IBC in about 5% and 4%, respectively [40]. Although invasive micropapillary carcinoma is known to often be accompanied by extensive lymphovascular invasion, this subtype does not seem to be overrepresented in IBC.

Lymphovascular invasion is a prerequisite for lymph node metastases to develop. Therefore, practically all patients with regional lymph node metastasis should have (had) lymphatic tumour emboli. However, this feature is not always seen in specimens of node-positive primary breast carcinomas. The discrepancy may be explained by a spatial and temporal distribution of the emboli: they might have been present at the time of histological assessment, but at areas different from those sampled; or alternately, they might

**Table 1**
Changes in the definition of IBC.

| Source | Clinico-pathologic entity | Browny induration | Erysipeloid edge | Diffuse erythema/ oedema | Extent | Usually no underlying palpable mass | Dynamics | Radiologic mass (possible) | Radiologic thickening of the skin | Embolization of dermal lymphatics | Dermal LVI not enough for diagnosis |
|---|---|---|---|---|---|---|---|---|---|---|---|
| AJCC TNM5 (1997) [18] | + | + | + | − | − | + | − | + | + | + | − |
| AJCC TNM6 (2002) [19] | + | − | − | + | majority of the breast | + | − | + | + | + | + |
| AJCC TNM7 (2010) [20] | + | − | − | + | at least 1/3 | + | quick | + | + | + | + |
| AJCC TNM8 (2016) [21] | + | − | − | + | at least 1/3 | + | rapid, <6mo | + | + | ± | + |
| UICC TNM6 [27] | − | + | + | − | diffuse | + | − | − | − | − | − |
| UICC TNM7 (2009) [28] | − | + | + | − | diffuse | + | − | − | − | − | − |
| UICC TNM8 [24] | − | + | + | − | diffuse | + | − | − | − | − | − |

have been present earlier in the course of the disease. Consequently, when lymphovascular invasion is identified, it may reflect its massive presence (when sampling any area would reveal the same presence) or a chance finding (when most other areas would lack the feature). Most IBC cases have extensive dermal lymphatic emboli, but some tumours without inflammatory signs do have extensive peritumoral lymphatic invasion, and the latter have still better disease free and overall survival [28], suggesting that dermal lymphatic invasion is not the only difference in IBC and non-IBC. Both increased lymphangiogenesis and angiogenesis have been documented in IBC, giving the increased vascular invasion a molecular background [41]. Colpaert et al. also demonstrated an increased level of angiogenesis in IBC versus non-IBC samples and suggested that increased angiogenesis in the IBC tumours was, for the most part, not stimulated by hypoxia but was due to a vasculogenic phenotype [42]. An IBC xenograft model, WIBC-9, has been extensively studied and revealed invasive ductal carcinoma pattern with a hypervascular structure of solid nests and marked lymphatic permeation in the overlying dermis [43,44]. WIBC-9 exhibited aneuploidy, HER2 gene amplification, and absence of hormonal receptors, which is consistent with IBC. In the central part of the solid nests, vasculogenic mimicry was observed, with an absence of endothelial cells. Vasculogenic mimicry was described in many aggressive tumours as blood vessels formed by tumour cells instead of endothelial cells [45,46]. Molecular analysis indicated the vascular phenotype of this xenograft, with expression of vascular markers such as Flt-1 and Tie-2, even in the areas that displayed vascular mimicry. This model was used to describe the vasculogenic phenotype of IBC, and suggested a connection between vasculogenic mimicry and angiogenesis [47]. Vasculogenic mimicry can also explain the metastatic route of IBC, and why IBC is so aggressive clinically.

Primary human IBC derived cell-line and xenograft derived-models have helped to clarify some aspects of the formation of dermal lymphatic emboli. Overexpression of the transmembrane adhesion protein E-cadherin was one of the factors identified as being responsible for the formation of such emboli; the E-cadherin effect could be reduced by downregulating the E-cadherin-catenin axis [48]. Another molecule with confirmed importance is MUC1, which is involved in tumour emboli binding to lymphovascular endothelial cells. The markedly decreased sialyl-Lewis x/a (sLex/a) carbohydrate ligand-binding epitopes on overexpressed MUC1 participate in the passive dissemination of emboli [49,50]. Schneider et al. also demonstrated that the unique pathogenic properties of IBC result in part from overexpression of the translation initiation factor eIF4G1. This overexpression leads to a specific increase in the translation of internal ribosomal entry site (IRES) containing mRNAs. Specifically, two such mRNAs, p120 catenin and VEGF, encode key proteins involved in the pathogenesis of IBC. The p120 catenin protein causes retention of E-cadherin at the cell surface and VEGF produces angiogenic effects and resistance to hypoxia. Silencing of eIF4G1 caused marked reduction in p120 catenin protein levels and cell surface associated E-cadherin expression in SUM149 cell-line cells. Ectopic overexpression of p120 catenin in eIF4G1 silenced cells was able to restore invasion, E-cadherin cell surface localization, tumour growth and hence ability to generate IBC mammospheres to the levels observed in controls [51].

## IBC and gene-expression profiles

In current clinical practice, commercially available gene expression profile (GEP) based diagnostic tests are deemed useful to tailor individual patients' treatment, i.e. to identify patients who would require aggressive systemic treatment and those who would not benefit from such an approach, especially in cases where traditional prognostic factors are borderline. Therefore, the indication to use gene-expression profiles in IBC is missing at the clinical level, which may explain the relative scarcity of data derived from GEPs.

The largest series assessing the composition of IBCs according to intrinsic subtypes on the basis of GEP comes from the World IBC Consortium [40]. After assessing 137 IBCs with the PAM-50 algorithm complemented with the additional identification of the claudin-low subtype, it became clear that all subtypes are represented: 26 (19%) showed luminal A and luminal B characteristics each, whereas 30 (22%), 24 (17%), 23 (17%) and 8 (6%) were of the HER2 enriched, basal-like, claudin-low and normal breast like types, respectively [40].

When the intrinsic subtypes are approached by immunohistochemistry (IHC), the match between the gene-expression derived subtypes (luminal A and B, HER-2 enriched, basal-like) and the differently defined IHC based groups (luminal A-like, luminal B-like, HER2(ER-negative) and triple negative) is less than perfect. Kertmen et al. suggested that IBC belonged to luminal A-like carcinomas as often as 35% (27/78) in a Turkish population, but their definition for luminal A was not provided, and may not have been restrictive enough [37]. To support this latter explanation (i.e. definition not restrictive enough), only 10% (7/67) of IBC in a Chinese population were classified as luminal A-like with the 2011 St Gallen IHC definitions (ER-positive, HER2-negative, Ki67<14% labelling) [52].

IBC is therefore a clinicopathologic entity that is not uniform in histologic type, grade, IHC phenotype, or GEP based intrinsic subtypes. The question therefore arises whether anything else distinguishes IBC from non-IBC. Possible approaches include the search of such distinguishing features in the tumours or the host (e.g. the immune response to cancer), methylation patterns or changes in expression of microRNAs.

When compared to non-IBCs, IBCs showed higher activation of 8 molecular pathways (CTNB, HER2, MYC, RAS, IFNα, IFNχ, TNFα and VEGF) along with lower activation of 4 pathways (ER, PR, p53 and TGFβ), whereas the remaining of the assessed activity pathways (AKT, E2F1, EGFR, PI3K, SRC, STAT3 and p63) showed no statistical differences [40]. Downregulation of the TGFβ pathway has also been related to the propensity of IBC to spread through the lymphatics [40]. A smaller series has pointed to relatively common alterations in other pathways, such as alterations in HER3 often coexisting with HER2 alterations [53]. A set of 78 transcription factors also showed difference in activation between IBCs and non-IBCs, including the hyperactivation of RELA (a nuclear factor kappa B – NFκB-component) in IBC [40]. This is in keeping with earlier and recent studies suggesting a role for NFκB-related genes in IBC [54,55]. However, differences observed between IBC and non-IBC are not all related to the inflammatory nature of IBC. When looking at specific genes that are uniquely expressed in IBC as compared to non-IBC, a set of 79 genes were identified as being uniquely specific for IBC, and their expression may be of help in the molecular definition of IBC and used as an IBC GEP classifier [40].

## Inflammation in IBC

Carcinogenesis, cancer growth and metastasis are closely linked to tumour microenvironment. The intrinsic link between inflammation and cancer is both an old and a very contemporary story. More than a century ago, Rudolf Virchow and colleagues hypothesized for the first time that inflammation was associated with tumours [56]. Nowadays it would be difficult to deal with cancer and skip the inflammatory process.

Modulation of inflammation and immunity is implicated in tumour growth and survival, but is also becoming a successful

therapeutic target with the promising results of clinical trials using immune checkpoint inhibitors in lung cancer and melanoma [57]. In breast cancer, too, the immune environment plays a role in aggressive molecular types, like basal-like and triple negative carcinomas [58]. The immune component is fully implicated in tumoural response to neoadjuvant chemotherapy [59]. Clinical trials to restore host immune response, like the ones targeting the PD1/PDL1 or the CTLA4 axis are currently running. Recent reports suggest that targeting protein glycosylation with a monoclonal antibody is a potential strategy to enhance immune checkpoint therapy in triple negative breast cancers [60]. Pathological guidelines to quantify tumour infiltrating lymphocytes have been published and updated, as this parameter is currently evaluated as a biomarker for including breast cancer patients in clinical trials [61,62].

As to the immune infiltrate in IBC, tumours seem to be relatively heterogeneous. A significant minority of IBCs (5/12; 95% confidence interval: 19–68%) displayed high rates of tumour infiltrating lymphocytes (TILs) according to the authors definition (>5% intratumoural area), which is different from the International TILs Working Group recommendation mandating at least 50% stromal TILs for a lymphocyte predominant breast carcinoma [61,62]. In keeping with results described in breast cancer in general, a low percentage of these lymphocytes belong to the regulatory FOX3P + T-cells, which are thought to represent a tumour promoting effect, and the majority are $CD8^+$ cytotoxic cells [53]. However, other IBC lack this degree of lymphocytic infiltration, leading to the conclusion that TILs are not responsible for the IBC phenotype.

Similarly to lymphocytes, according to the immune-editing theory of cancer, tumour associated macrophages (TAMs) may either inhibit or promote cancer progression [61], and the tumour promoting subset is more prevalent in breast carcinomas; IBCs have relatively high levels of TAMs [63]. Inflammatory cytokines have also been reported to be released at high levels in IBC. As mentioned earlier, for example, NFκB and related genes are often upregulated in IBC and these genes play an important role in immunity, and also in the increased secretion of inflammatory cytokines like IL6 or IL8 [63]. Cycloxygenase-2 (COX2) levels and/or prostaglandin E2 (the main catalytic product of COX2) levels are elevated in a range of tumours, including a subset of breast cancers. Elevated COX2 levels are part of the molecular IBC signature identified by the World IBC Consortium and are, therefore, also part of the inflammatory changes associated with IBC. The role of extrinsic factors in the tumour microenvironment, like TILs, TAMs and cytokines may help to account for the differences in behaviour between IBC and non-IBC, and other microenvironmental factors provide an avenue for novel therapeutics.

Inducible nitric oxide synthase (NOS2) is an enzyme involved in the production of nitric oxide (NO). It is upregulated in a high proportion of ER-negative tumours with poor prognosis. Stimuli like interferon-α or hypoxia result in overexpression of NOS2, and NOS2 is downstream related to the release of inflammatory mediators linked to poor outcome in breast cancer (and also found to be elevated in IBC), like IL6 or IL8. High levels of NOS2 and NO have also been related to tumour growth and metastasis as well as chemoresistance to paclitaxel [64]. Although NOS2 emerged as an attractive biomarker of poor prognosis, and is linked to inflammation, it has not been directly linked to IBC, and is not among the IBC signature genes described by the World IBC Consortium [40].

## Cancer stem cells

Cancer stem cells (CSCs) are a subpopulation of tumour cells that exhibit specific features, which explain cellular heterogeneity of tumours. They are responsible for a hierarchical organization of tumour tissues where several subpopulations of self-renewing breast CSCs sustain the long-term oligoclonality of the neoplasm [65]. Moreover, these cells are responsible for recurrence and metastasis [66] and they have been found to be mostly resistant to conventional therapies compared with their non-tumorigenic progeny [67].

IBC cells displayed a CSC subpopulation, which may contribute to the aggressive and motile characteristics of IBC [66]. In particular, SUM-149 IBC cell line cells display $CD44^+/CD24^{-/low}$ stem cell surface markers, as well as aldehyde dehydrogenase-1, a maker of CSC [66,68]. When CSCs with this phenotype were injected into mice, they were highly tumorigenic [69]. The patient derived xenograft model of IBC (MARY-X) exhibits this phenotype, along with the unique stem cell marker CD133 [70]. Therapeutically, targeting of this CSC phenotype within IBC cells via the Notch pathway inhibition results in a significant reduction in anchorage independent growth of SUM-190 and SUM-149 IBC cell line cells [71]. The sonic hedgehog pathway, a central pathway in stem cell biology, is differentially regulated in IBC patients, and the downstream zinc-finger transcription factors of the glioma associated oncogene (GLI) are the final steps in the hedgehog pathway. Modulation of GLI1 in IBC suggests it has a role in cell proliferation, survival and migration, and this supports the feasibility of targeting GLI1 as a potential therapeutic strategy for IBC patients [72].

## Concluding remarks

Despite the characteristic and distinguishing clinical presentation, IBC is not a homogeneous disease. Often it is of the type associated with a poor prognostic profile (no special type cancer of high grade, belonging to the ER-negative subset and/or the HER2-positive subset), examples with different histologic type, grade, receptor status, intrinsic subtype are also represented in this clinico-pathologic entity. There are several targetable changes in IBC, some of which represent molecular pathways of carcinogenesis while others represent pathways of inflammation and still others are involved in different other biological processes. However, there has been no unique characteristic identified for these tumours that would allow a single therapeutic intervention. As IBC is a rare manifestation of breast cancer, specific clinical trials are more difficult to be organized, and preclinical studies are important both to advance our understanding of IBC pathophysiology and to select which clinical trials should be favoured over others. As the tumoural microenvironment is very important in IBC, and may be a key to understand its clinical presentation and propose new therapeutic modalities, models that include the tumour stroma [73] might be of greater value than classical IBC cell lines in the study of this entity. It has recently become possible to grow organoids from breast cancer [74], that may be useful in this respect, especially when co-cultured with inflammatory cells or stromal cells, or to use the new generation of humanized patient derived xenografts with immune cells in mice.

## Conflict of interest statement

The authors have no conflict of interest to disclose.

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